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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,644	02/21/2002	Hiroaki Yamamoto	14879-100001/ D1-A0103-US	1965

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EXAMINER
LUCAS, ZACHARIAH

ART UNIT	PAPER NUMBER
1648	14

DATE MAILED: 08/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,644	YAMAMOTO ET AL.	
	Examiner	Art Unit	
	Zachariah Lucas	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *4-15 and 18-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,16 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Claims 4-15, and 18-42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 12.

Claims 1-3, 16, and 17 are pending and under consideration.

Claim Rejections - 35 USC § 101

2. Claims 16 and 17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

These claims read on variants and fragments of the protein of SEQ ID NO: 2. SEQ ID NO: 2 is an enone reductase protein for which the Applicant has identified uses in the processing of chemical intermediaries. App., page 1. However, these uses require the ability of the protein to reduce the double carbon bond of α,β-unsaturated ketone. No other utility for the claimed proteins has been provided. However, as written, the claims read both on proteins with the enone reductase activity of SEQ ID NO: 2, and on proteins without such activity. The claims are therefore rejected as reading on inventions for which no utility has been asserted.

Claim 16 and 17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim reads on an enone reductase that "is derived from an organism or the genus Kluyveromyces." It is unclear what is meant by the phrase "derived from." More specifically, it is unclear whether this claim is limited to enone reductases that may be isolated from the identified fungi, or if the claims include non-natural variants of such proteins.

5. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim reads on "a substantially purified polypeptide encoded by the nucleic acid of claim 6." Claim 6 described nucleic acids encoding proteins that comprise the sequences of SEQ ID NO: 2 with one or more additions, deletions, or substitutions(i.e. variants of SEQ ID NO: 2),, polypeptides of at least 60% identity to SEQ ID NO: 2(also discussed as variants to SEQ ID NO: 2), or fragments of the protein, wherein the variants and fragments are functionally equivalent to the protein of SEQ ID NO: 2.

However, the claim does not identify a function of the protein of SEQ ID NO: 2 such that one of ordinary skill in the art would recognize what proteins are "functionally equivalent"

to that protein. It is suggested that the applicant amend the claim to clarify that these variants have the enone reductase activity of SEQ ID NO: 2.

6. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This claim is rejected because it describes a polypeptide encoded by the nucleic acid of claim 6, which describes a nucleic acid that will hybridize to the sequence of SEQ ID NO: 1, that encodes for SEQ ID NO: 2, under stringent conditions. This claim is rejected because it is unclear what is meant by the term "stringent conditions." Because the Applicant has not defined what is meant by this phrase, those in the art would not be able to determine the scope of what is being claimed.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This claim reads, in part, on proteins encoded by "a nucleic acid that hybridizes under stringent conditions with a nucleic acid consisting of the nucleotide sequence of SEQ ID NO: 1, and that encodes a protein functionally

equivalent to a protein consisting of the amino acid sequence of SEQ ID NO:2." The specification discloses SEQ ID NO: 1 as encoding SEQ ID NO: 2. See, page 12, lines 4-5. If SEQ ID NO: 1 encodes the protein of SEQ ID NO: 2, then a nucleic acid that hybridizes to SEQ ID NO: 1, which would be a complement of that sequence, would not also encode SEQ ID NO: 2, or a derivative thereof. Because a nucleic acid that hybridizes to SEQ ID NO: 1 would not encode a protein of, or derived from, SEQ ID NO: 2, and because the Applicant has not defined, or described a use, or function of, proteins that could be encoded by such a sequence, the Applicant is not enabled for these proteins.

9. Claims 3 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for proteins of SEQ ID NO: 2, does not reasonably provide enablement for variants or fragments of this protein which are functional equivalents of SEQ ID NO: 2. For the purposes of this rejection, claim 16 is being read as though the fragments and variants are required to have the enone reductase activity of SEQ ID NO: 2. Claim 3 is being interpreted as including non-natural derivatives of enone reductases that may be isolated from Kluyveromyces fungi. Claim 16 is being treated as representative of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary,

(2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

As indicated above, claim 16 reads on any fragments or variants of the protein of SEQ ID NO: 2 wherein the fragments or variants have the enone reductase activity of SEQ ID NO: 2. However, while the claim broadly includes all such polypeptides, the application neither discloses any examples of, nor provides any guidance that would lead those in the art towards, such polypeptides. Given that SEQ ID NO: 2 comprises over 350 amino residues, and that multiple variations of the protein may be made with reference to any one of these residues, the claims cover a large number of possible variants.

It is known in the art of protein substitution that, while proteins tend to be tolerant of amino acid substitutions, the effects that a mutation of any particular residue will have on the function of a protein are largely unpredictable. See Bowie et al., Science, 247:1306-10. Thus, without some guidance, such as an identification of residues or sequences required for protein function, those in the art would not be able to determine what variations may be made to a protein without a loss of protein activity. No such identifications have been made in the present application. Because the Applicant has not disclosed any examples of the claimed variants or fragments, and because the application does not provide any guidance that would lead those in the art towards such polypeptides, the Applicant is not enabled to the extent that the claims read on such polypeptides. Because claim 3 requires that the derivate have more than just the enone

reductase activity of SEQ ID NO: 2, and because the Applicant does not teach any correlation between the protein characteristics identified in either claim 3 or claim 1 (from which it depends) the unpredictability referred to with reference to claim 16 applies to a higher degree with regards to claim 3.

In view of broad scope of the claims, the unpredictability in the art, the lack of working examples, and the lack of guidance leading those in the art to such examples, the Applicant has not provided an enabling disclosure to the extent that the claims read on any fragment or variant of the protein of SEQ ID NO: 2.

10. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims read on any enone reductase that meets certain physical property limitations.

The following quotation from section 2163 of the Manual of Patent Examination Procedure is a brief discussion of what is required in a specification to satisfy the 35 U.S.C. 112 written description requirement for a generic claim covering several distinct inventions:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406.

> A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Thus, when a claim covers a genus of inventions the specification must provide written description support for the entire scope of the genus. Support for a genus is generally found where the applicant has provided a number of examples sufficient so that one in the art would recognize from the specification the scope of what is being claimed. Such support may also be provided by an association of product structure to a claimed function, and by the identification of relevant identifying characteristics.

In the present case, the Applicant has identified the claimed genus through identification of chemical properties of the disclosed protein. However, the Applicant has provided only one example of a protein with the desired characteristics- the protein of SEQ ID NO: 2. See, App., pages 29-31. While three other proteins are disclosed as enone reductases, these proteins have not been shown to have the other chemical properties of the claimed invention. Nonetheless, the claims are written such that they indicate an intent to cover more than just SEQ ID NO: 2. This indication can be seen most clearly in claim 3, which further limits the class of claimed enone reductases of claim 1 to those that may be "derived from an organism of the genus Kluyveromyces." Claim 3 thereby indicates that claim 1 reads on enone reductases other than those that may be derived from Kluyveromyces, the fungal genus from which the protein of SEQ ID NO: 2 may be isolated.

Each of these other 3 other enone reductases identified by the Applicant shares, respectively, 51, 52, and 53% identity with the protein of SEQ ID NO: 2. However, while the Applicant has shown that these proteins share some sequence homology, and that they have

enone reductase activity, the Applicant has not shown that the disclosed physical/chemical properties of SEQ ID NO: 2 is common to all of the proteins.

In the art, protein activity is known to be highly dependent on the amino acid sequence of the proteins. See Abstract, Bowie et al., Science 247:1306-1310. Likewise, the structure and stability of the proteins, each related to protein function, are also influenced by the sequence. See e.g., id., at page 1307, first column. Thus, just a protein function is highly dependant on the sequence, so are the other chemical properties of the proteins. Because the other enone reductases disclosed by the Applicant share only a 50% identity with SEQ ID NO: 2, there is an indication that these proteins have different chemical properties from those of SEQ ID NO: 2. Thus, the Applicant has not provided adequate written descriptive support for claims to enone reductases, other than SEQ ID NO: 2, that have the identified properties.

Furthermore, in the event that claim 3 is intended to include variants of enone reductases that are produced by fungi of the genus Kluyveromyces, the claim is also rejected because the Applicant has not provided any examples, or other guidance, as to such derivates such that all of the chemical properties identified in claim 1 are maintained. Because the Applicant has not correlated any of these properties with any structural characteristic of the claimed proteins, those in the art would not be able to identify such enone reductases, or to distinguish them from other enone reductases that do not have the identified characteristics.

11. Claims 1-3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the enone reductase of SEQ ID NO: 2, does not reasonably provide enablement for other enone reductases that have the chemical properties according to the

identified claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The claims have been described above. They read on any enone reductase with the chemical properties in the identified claims.

However, as indicated above, the Applicant has shown only one protein with the disclosed properties. The Applicant has also disclosed three other proteins that have enone reductase activity, but have not been shown to share any of the other chemical properties of SEQ ID NO: 2. Further, because the art recognizes that the functional properties of proteins varies with their sequences, and because these other proteins share only 50% identity with SEQ ID NO: 2, and do not appear to share have any conserved regions, there is no indication that these other sequence do have the identified properties. Thus, the Applicant has provided only one known example of the claimed invention, and has otherwise provided only examples of other enone reductases that may fall within the claims.

As indicated above, a protein's function, and other properties, are dependant upon the protein's amino acid sequence. However, at present, those in the art are not able to determine such properties from the protein's sequence alone. See, Bowie et al, Science, 247:1306-1310, page 1306 left column. Because the Applicant has not associated the identified properties with any specific residues or motifs in the enone reductase of SEQ ID NO: 2, the Applicant has not provided much guidance to those in the art as to how to identify other such enone reductases. In view of the lack of guidance provided, and the unpredictability in the art, the Applicant has not provided an enabling disclosure for the full scope of the claimed invention.

12. Claims 3, 16, and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims describe a genus of variants and fragments of the protein of SEQ ID NO: 2, wherein said variants or fragments are functionally equivalent (or have all of a set of chemical properties of) to the disclosed protein.

The requirements for the 35 U.S.C. 112 written description requirement regarding a genus of inventions have been described above. In the present claims, the Applicant has chosen to identify the genus by a combination of a functional characteristic (the enone reductase activity) with a structural characteristic (sequence identity with SEQ ID NO: 2). However, while the Applicant has shown that SEQ ID NO: 2 has the identified activity, there is no indication in the application as to what portions, or residues, in the protein are necessary to the proteins function. I.e., the Applicant has not disclosed any correlation between the identified structure and the claimed function. In the absence of such correlation, the Applicant has not shown those in the art that the Applicant was in possession of the claimed genus, or provided sufficient information such that those skilled in the art could identify the members of the claimed genus.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Shimoda et al., Phytochemistry 49(1):49-53, Wanner and Tressl, Eur. J. Biochem 255:271-78, and Kawai et al., Tetrahedron Letters 39:5225-28 (all of record in the IDS filed on July 30, 2002). As indicated above, claim 16 reads on the polypeptides encoded by the nucleic acids of claim 6. Claim 6 reads in part, on nucleic acids "encoding a protein that comprises the amino acid sequence of SEQ ID NO: 2, in which one or more amino acids are substituted, deleted, inserted and/or added and that is functionally equivalent to a protein consisting of the amino acid sequence of SEQ ID NO: 2." The claim neither sets any structural limitations on the protein so encoded (e.g. a minimum sequence identity or a maximum number of substitutions, deletions, or additions). Thus, the proteins in this case are limited solely by the functional language. However, as indicated above, the claim does not identify what is meant by the term "functionally equivalent." Thus, for the purposes of this rejection, the claim is being read as including any protein with enone redutase activity.

Each of the above references identifies one or more proteins with enone reductase activity, wherein the proteins reduce carbon-carbon double bonds. It is noted that each of the Wanner and the Shimoda references teach protein with a different disclosed optimum ph from the protein of SEQ ID NO: 2. However, as the Applicant has not identified what is meant by the term "functionally equivalent," this is not deemed sufficient to distinguish the art from the claims as presently drafted.

Conclusion

15. No claims are allowed.

16. The protein of SEQ ID NO: 2 appears to be free of the art.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachariah Lucas whose telephone number is 703-308-4240. The examiner can normally be reached on Monday-Friday, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 703-308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Z. Lucas
Patent Examiner
July 29, 2003

JAMES HOUSEL 8/8/03
SUPERVISORY PATENT EXAMINER
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